



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
University Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2015

---

## **Specific skin infiltration as first sign of localized stage Hodgkin's lymphoma involving an epitrochlear node**

Llamas-Velasco, Mar ; Fraga, Javier ; Pérez-Gala, Silvia ; Cannata, Jimena ; Kempf, Werner ; Adrados, Magdalena ; García-Diez, Amaro

**Abstract:** Cutaneous manifestation as the first sign of Hodgkin lymphoma (HL) is very rare and diagnostically challenging; especially, because the clinical presentation of specific skin involvement by HL is polymorphous. We present a 44-year-old man with erythematous indurate papules and plaques in the right forearm and arm where skin biopsy showed an HL. He also has an enlarged epitrochlear node, and later histopathologic study confirmed the diagnosis of HL subtype-mixed cellularity. Immunohistochemical stains in both biopsies showed that the atypical cells were positive for CD30 and CD15, and negative for CD20 and CD3. PAX5 stained the nuclei of the atypical large lymphoid cells weakly and Oct-2 staining was negative in the atypical cells. EBER and LMP1 protein were negative in both biopsies. Epitrochlear involvement in HL, like in our case, is a rare event (<1%). We reviewed data about prognosis, clinical appearance, and treatment of all the cases of HL specific skin involvement published after Sioutos et al, emphasizing the cases where HL specific skin involvement was the first sign of the disease as in our patient.

DOI: <https://doi.org/10.1097/DAD.0000000000000127>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-108439>

Journal Article

Published Version

Originally published at:

Llamas-Velasco, Mar; Fraga, Javier; Pérez-Gala, Silvia; Cannata, Jimena; Kempf, Werner; Adrados, Magdalena; García-Diez, Amaro (2015). Specific skin infiltration as first sign of localized stage Hodgkin's lymphoma involving an epitrochlear node. *American Journal of Dermatopathology*, 37(6):499-502.

DOI: <https://doi.org/10.1097/DAD.0000000000000127>

# Specific Skin Infiltration as First Sign of Localized Stage Hodgkin's Lymphoma Involving an Epitrochlear Node

Mar Llamas-Velasco, MD, Javier Fraga, MD, PhD,\* Silvia Pérez-Gala, MD,† Jimena Cannata, MD,‡ Werner Kempf, MD, PhD,†§ Magdalena Adrados, MD, PhD,\* and Amaro García-Diez, MD, PhD†

**Abstract:** Cutaneous manifestation as the first sign of Hodgkin lymphoma (HL) is very rare and diagnostically challenging; especially, because the clinical presentation of specific skin involvement by HL is polymorphous. We present a 44-year-old man with erythematous indurate papules and plaques in the right forearm and arm where skin biopsy showed an HL. He also has an enlarged epitrochlear node, and later histopathologic study confirmed the diagnosis of HL subtype–mixed cellularity. Immunohistochemical stains in both biopsies showed that the atypical cells were positive for CD30 and CD15, and negative for CD20 and CD3. PAX5 stained the nuclei of the atypical large lymphoid cells weakly and Oct-2 staining was negative in the atypical cells. EBER and LMP1 protein were negative in both biopsies. Epitrochlear involvement in HL, like in our case, is a rare event (<1%). We reviewed data about prognosis, clinical appearance, and treatment of all the cases of HL specific skin involvement published after Sioutos et al, emphasizing the cases where HL specific skin involvement was the first sign of the disease as in our patient.

(*Am J Dermatopathol* 2014;0:1–4)

## INTRODUCTION

Nonspecific cutaneous manifestations of Hodgkin disease/lymphoma (HL) are quite frequent,<sup>1,2</sup> with 17%–53% of patients developing any of them<sup>2,3</sup> but the incidence of specific cutaneous HL varies between only 0.5% and 7.5%.<sup>3</sup> Cutaneous manifestation as the first sign of HL is very rare and diagnostically challenging; especially, because the clinical presentation of specific skin involvement by HL is polymorphous. The most common ones are papular or nodular lesions.<sup>1,4</sup> We report a patient with specific skin involvement by HL as the first disease presentation of a localized HL involving an epitrochlear lymph node and lacking association with Epstein–Barr virus (EBV).

## CASE REPORT

A 44-year-old white man with no contributory medical history complained of a plaque on the lateral aspect of forearm that appeared a year earlier. Five months later, similar papules and plaques have

progressively appeared on his ipsilateral arm. All lesions were stable and asymptomatic. The patient denied other skin or mucosal lesions, fevers, chills, weight loss, or other systemic symptoms. On physical examination, he presented with an erythematous indurated plaque of 1.7 × 2 cm on the right forearm and several similar smaller papular lesions on his right arm with a sporotrichoid pattern (Fig. 1A). A mobile and consistent epitrochlear ipsilateral enlarged lymph node with 2 cm was found (Fig. 1B). A skin biopsy showed a dense nodular infiltration by lymphocytes and histiocytes, and scattered eosinophils arranged throughout the dermis. Those cells were mixed with large lymphoid cells with hyperchromatic and irregularly shaped nuclei representing Reed–Sternberg cells (Figs. 2A, B). An epitrochlear lymph node biopsy demonstrated features of classic HL of mixed cellularity subtype in the interfollicular region (Figs. 3A, B). Immunohistochemical stains in both biopsies showed that the atypical cells were positive for CD30 and CD15, and negative for CD20 and CD3 (Figs. 2C, D, 3C, D). PAX5 stained the nuclei of the atypical large lymphoid cells weakly and Oct-2 staining was negative in the atypical cells (Fig. 4). EBER and LMP1 protein were negative in both biopsies. ALK staining was negative in node.

Viral serologies were negative for HIV but positive for EBV. A computed tomography examination of the thorax, abdomen, and pelvis disclosed axillary enlarged lymph nodes. Examination of the bone marrow was normal. He was diagnosed with HL at Cotswolds stage IIA<sub>E</sub> and treated with 6 cycles of ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), which resulted in a complete remission. The patient was disease-free after a follow-up of 38 months.

## DISCUSSION

We had reviewed the literature on HL specific skin involvement, and we found 20 articles reporting 26 cases including ours<sup>1,3,5–22</sup> in the last decade because we agree with other authors who consider the cases described by Sioutos et al as the first well-defined cases of HL specific to skin involvement. All the cases of HL specific to skin involvement as the first sign of the disease as in our patient can be seen in Table 1. We did not include series without reporting HL stage or individual data of the patients.

In the rest of the reported cases, HL specific to skin involvement was a sign of relapse of a previously known HL. Primary cutaneous HL is exceedingly rare and only a few well-documented cases have claimed this diagnosis,<sup>5,6,9,12,14,15</sup> some of them with lately systemic involvement. Within these cases, three of the cases reported by Sioutos et al could be more accurately considered lymphomatoid papulosis because of their waxing and waning chronic clinical course.

Related to prognosis, skin specific involvement in HL is considered in most of the reports as a prognostically

From the Departments of \*Pathology, †Dermatology, and ‡Hematology, Hospital Universitario De “La Princesa”, Madrid, Spain; and §Kempf und Pfaltz, University Hospital Zürich, Zurich, Switzerland.

The authors declare no conflicts of interest.

Reprints: Mar Llamas Velasco, MD, C/Diego de León 62, CP28006 Madrid, Spain (e-mail: mar.llamasvelasco@gmail.com).

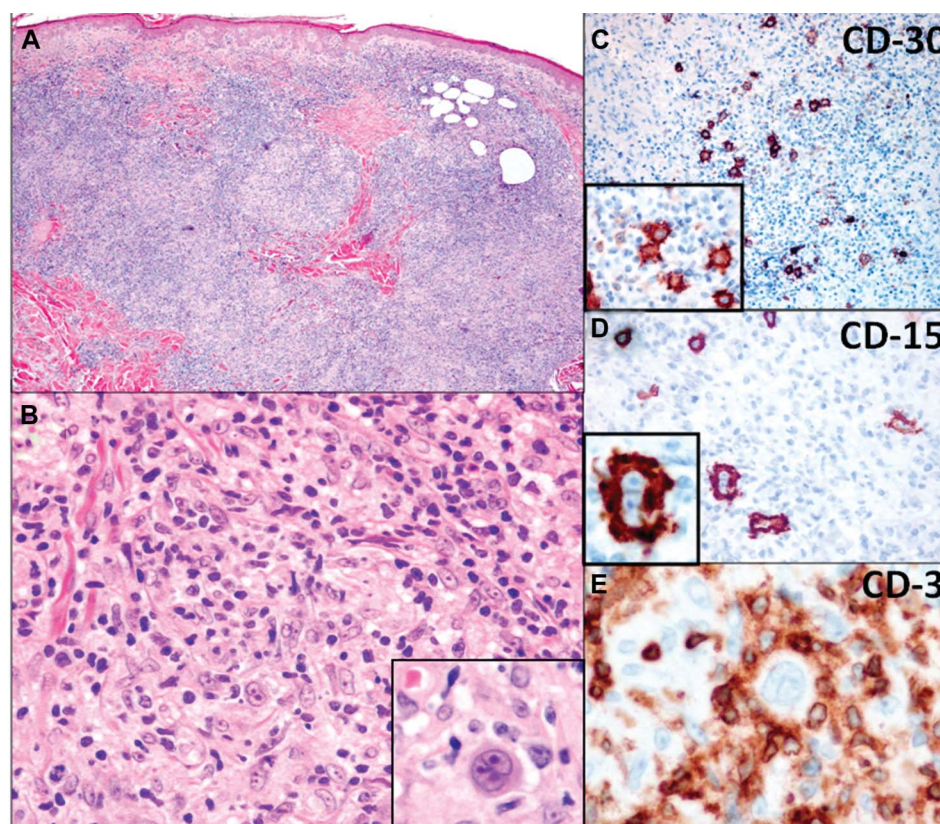
© 2014 Lippincott Williams & Wilkins



**FIGURE 1.** A, Indurated, lobulated erythematous plaques with well-defined borders and sporotricoid pattern located in the right arm and forearm. B, Epitrochlear enlarged node.

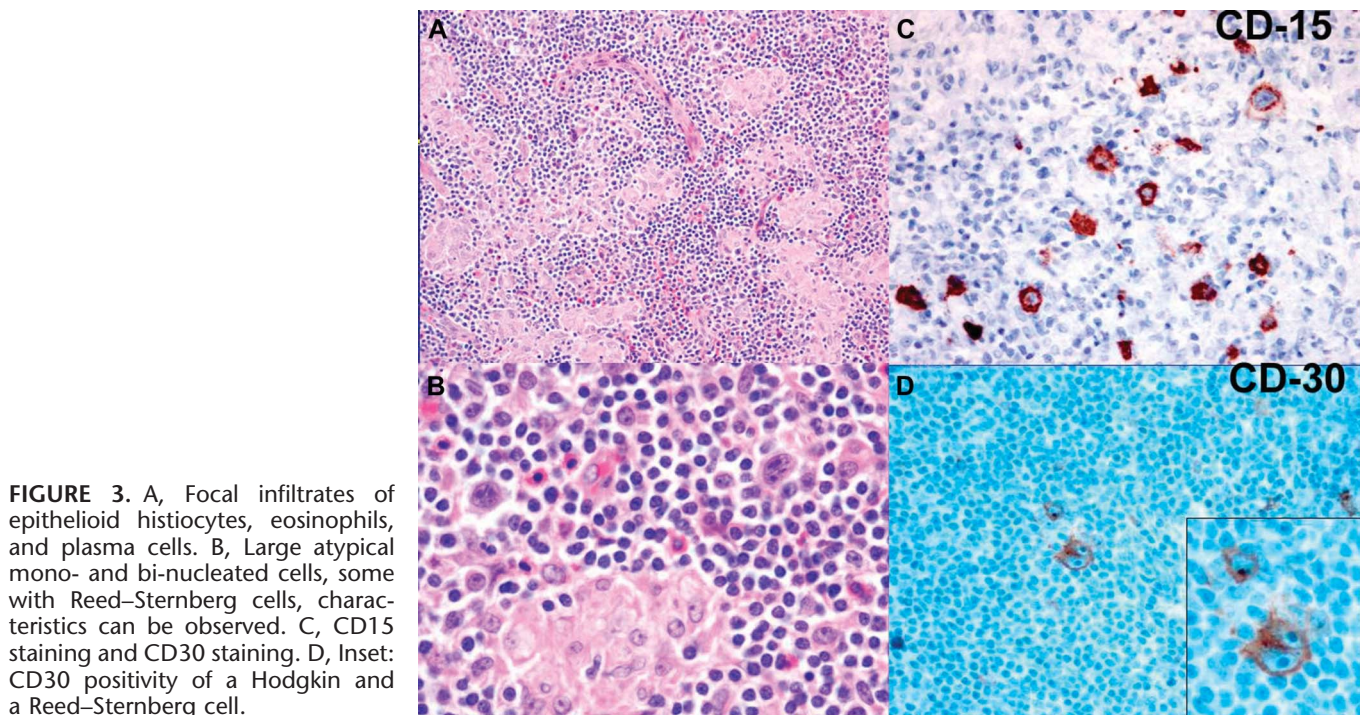
unfavorable sign indicating a stage IV. In our review, 8 of the 18 cases of HL specific skin involvement as the first sign of disease presented with III or IV stages but only 2 deaths were reported. Only one additional death was added from the rest of the cases. Unfortunately, immunohistochemistry panels

cannot differentiate primary and secondary cutaneous HL,<sup>23</sup> and the literature review indicates that it is not possible to determine whether the course of the disease in patients with HL with skin involvement, primary or not, will be severe or mild.<sup>4</sup> Recently, new markers as paired box gene 5 (PAX5),



**FIGURE 2.** A, Hematoxylin and eosin (HE), ×10. Nodular infiltrates with a granulomatous pattern. B, HE, ×20. Lymphocytes, histiocytes, and eosinophils mixed with big cells with basophilic cytoplasm and 2 or bigger nuclei with patent eosinophilic nucleoli can be identified as Reed-Sternberg cells. C–E, CD15 and CD30 positivity of the Reed-Sternberg cells and Reed-Sternberg cells rimmed by T cells with CD3 immunostaining.





**FIGURE 3.** A, Focal infiltrates of epithelioid histiocytes, eosinophils, and plasma cells. B, Large atypical mono- and bi-nucleated cells, some with Reed-Sternberg cells, characteristics can be observed. C, CD15 staining and CD30 staining. D, Inset: CD30 positivity of a Hodgkin and a Reed-Sternberg cell.

octamer-binding transcription factor-2 (Oct-2), and B-cell Oct-binding protein 1 (BOB-1) have been described to demonstrate B-cell lineage of HD<sup>24</sup> and to exclude histopathologic mimickers. PAX5 staining in cutaneous HD is weaker in the large atypical nuclei compared with the surrounding reactive B cells as in our case, and it helped to exclude a CD15<sup>+</sup> anaplastic large cell lymphoma.<sup>23</sup> Negative staining for CD20 and Oct-2 and the weak staining of PAX5 also argue against a B-cell non-HL.

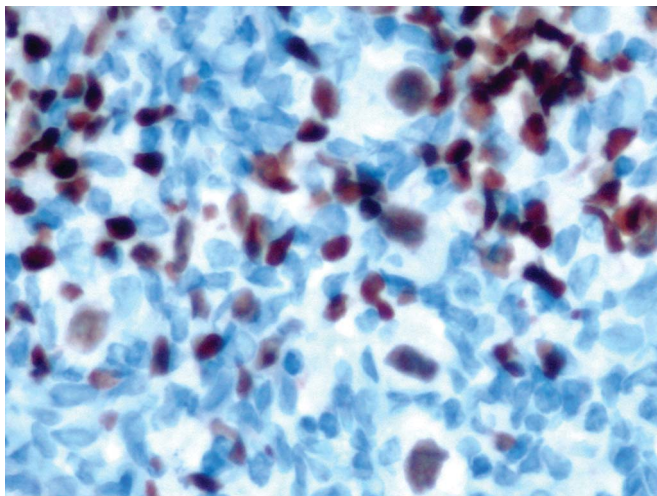
The distribution of the lesions in our patient confirms to the most frequently reported mechanism of skin involvement; by HL that is in proximity to the involved lymph nodes

because of retrograde lymphatic spread. Both direct extension from an underlying affected node and hematogenous dissemination have been also described.<sup>12</sup>

Epitrochlear involvement in HL, like in our case, is a rare event (<1%), although it has similar prognosis to that of other HL locations if appropriately treated.<sup>25</sup>

Finally, in North America and western Europe, 30%–50% of HL is associated with EBV, with a rate of up to 90% in mixed cellularity subtype.<sup>6</sup> There are several cases of EBER and LMP1 positive HL<sup>6,12</sup> that strongly favor HL diagnosis over CD30<sup>+</sup> lymphoproliferative disorders.<sup>6</sup> The lack of association with EBV in our patient is an infrequent feature of HL,<sup>6</sup> and is particularly diagnostically challenging in separating HL from cutaneous CD30<sup>+</sup> lymphoproliferative disorders. The lack of spontaneous regression of the lesions in our case argues against lymphomatoid papulosis. The phenotype of the large atypical CD30<sup>+</sup> cells in our patient with weak expression of the B-cell marker Pax5 and detection of nodal HL excludes the diagnosis of a primary cutaneous anaplastic large-cell lymphoma.

In summary, our case is noteworthy because skin lesions were the first site of presentation and skin biopsy led to the diagnosis of HL, although our case is rather a secondary HL with nodal epitrochlear involvement. Although cutaneous HL is rare, especially in localized stages, and the prevalence of specific secondary cutaneous HL seems to be diminishing, probably because of the advent of better therapy,<sup>3</sup> clinicians and pathologists should be aware of this rare manifestation of HL that first presents in the skin to identify early underlying HL. In addition, epitrochlear lymph node involvement has not been previously reported in patients with HL with skin involvement.



**FIGURE 4.** PAX 5 staining showing positivity in enlarged atypical lymphocytes.

**TABLE 1.** Reported Skin Involvement as First Sign of HL in the Last 10 years

Author	Age/ Gender, yr	Clinic	Location	Node/Megaly	Stage	Treatment	Response
Our case	44/M	P and PI	R. forearm	Epithroclear	IIE	AVBD	CR after 38 m
Vieites et al <sup>15</sup>	74/M	N	Scalp	None	IE	Lomustina, etoposide, prednisone	CR after 10 m
Pranteda et al <sup>14</sup>	10/M	P and N	R. back	None	IE	RT	CR after 20 mo
Hsia et al <sup>13</sup>	54/M	Ulcerated PI	L. gluteal area	Generalized	IIIB	AVBD	CR
Khalifeh et al <sup>12</sup>	67/M	Solitary PI	Occipital	Paraesophageal and bronchopulmonary/none	IV	AVBD	PR
Mukesh et al <sup>11</sup>	59/M	P and PI	Flank, feet, inner R. thigh	None	IE	AVBD	CR after 3 yrs
Balighi et al <sup>18</sup>	15/M	Ulcerated PI	B. Axillar	Generalized/splenomegaly	IV	COPP	CR after 9 mo
Miyoshi et al <sup>10</sup>	44/M	N	L. lower back	Paraortic/ hepatosplenomegaly	IV	Etoposide, ifosfamide, vindesine + electron beam	No response, death 5 mo later
Erkiliç et al <sup>22</sup>	25/F,	Ulcer	Neck	Generalized/splenomegaly (both)	IIIBE	EBVD	CR after 2 yrs
	19/F	Subcutaneous mass	Neck	Generalized/splenomegaly (both)	IIIBE	ABVD	CR after 3 yrs
De Grip et al <sup>20</sup>	34/F	Sinus	Neck	Tracheoesophageal fistula	III/IV	Unknown	Unknown
Guitart and Fretzin <sup>9</sup>	86/M	T	L. ankle	None/none	IIB	RT	No response, death in few months
Takagawa et al <sup>7</sup>	71/M	N	Supraclavicular area	Left supraclavicular/none	IV	Surgery and COPP	CR
Sioutos et al <sup>5</sup>	54/M	N	L. leg	None	IE	RT	CR for 6 yrs
	52/M	T and P	R. forearm	None	IE	None	RL
	17/M	N	Trunk	None	IE	Topical CT	RL
	50/M	N	R. thigh	None	IE	MOPP-ABVD	CR
	45/F	N	Forearm and legs	None	IE	Multiple chemotherapy	CR

Clinic—N, Nodules; P, papules; PI, plaques; T, Tumor.

Location—B, Both; L, Left; R, Right.

Treatment—AVBD: Adriamycin, vinblastine, bleomycin, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisolone; CT, corticosteroids; RT, radiotherapy.

Response—CR, complete response; PR, partial response; RL, recurrent lesions.

EBVD, epirubicin, bleomycin, vinblastine and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine, prednisone.

## REFERENCES

- Perifanis V, Sfikas G, Tziomalos K, et al. Skin involvement in Hodgkin's disease. *Cancer Invest.* 2006;24:401–403.
- Hayes TG, Rabin VR, Rosen T, et al. Hodgkin's disease presenting in the skin: case report and review of the literature. *J Am Acad Dermatol.* 1990;22:944–947.
- Introcaso CE, Kantor J, Porter DL, et al. Cutaneous Hodgkin's disease. *J Am Acad Dermatol.* 2008;58:295–298.
- Smith JL Jr, Butler JJ. Skin involvement in Hodgkin's disease. *Cancer.* 1980;45:354–361.
- Sioutos N, Kerl H, Murphy SB, et al. Primary cutaneous Hodgkin's disease. Unique clinical, morphologic, and immunophenotypic findings. *Am J Dermatopathol.* 1994;16:2–8.
- Kumar S, Kingma DW, Weiss WB, et al. Primary cutaneous Hodgkin's disease with evolution to systemic disease. Association with the Epstein-Barr virus. *Am J Surg Pathol.* 1996;20:754–759.
- Takagawa S, Maruyama R, Yokozeki H, et al. Skin invasion of Hodgkin's disease mimicking scrofuloderma. *Dermatology.* 1999;199:268–270.
- Jurisc V, Bogunovic M, Colovic N, et al. Indolent course of the cutaneous Hodgkin's disease. *J Cutan Pathol.* 2005;32:176–178.
- Guitart J, Fretzin D. Skin as the primary site of Hodgkin's disease: a case report of primary cutaneous Hodgkin's disease and review of its relationship with non-Hodgkin's lymphoma. *Am J Dermatopathol.* 1998;20:218–222.
- Miyoshi I, Daibata M, Fujishita M, et al. Cutaneous involvement in Hodgkin's disease. *Intern Med.* 2007;46:73.
- Mukesh M, Shuttleworth D, Murray P. Primary cutaneous Hodgkin's lymphoma. *Clin Exp Dermatol.* 2009;34:e673–e675.
- Khalifeh I, Hughey LC, Huang CC, et al. Solitary plaque on the scalp as a primary manifestation of Hodgkin lymphoma: a case report and review of the literature. *J Cutan Pathol.* 2009;36(suppl 1):80–85.
- Hsia CC, Howson-Jan K, Rizkalla KS. Hodgkin lymphoma with cutaneous involvement. *Dermatol Online J.* 2009;15:5.
- Pranteda G, Osti MF, Cox MC, et al. Primary cutaneous Hodgkin lymphoma. *J Am Acad Dermatol.* 2010;63:e52–e53.
- Vieites B, Avila R, Biscuola M, et al. Cutaneous Hodgkin-type lymphoproliferative lesion associated with immunomodulatory therapy for ulcerative colitis. *J Cutan Pathol.* 2011;38:443–447.
- Lowe GC, Hocker TL, Comfere NI, et al. Skin involvement with Hodgkin disease: a rare condition late in the course of Hodgkin lymphoma. *Am J Hematol.* 2013;88:979.
- Gru AA, Lu D. Concurrent malignant melanoma and cutaneous involvement by classical Hodgkin lymphoma (CHL) in a 63 year-old man. *Diagn Pathol.* 2013;8:135.
- Balighi K, Lajevardi V, Moeineddin F, et al. Scrofuloderma-like lesions in a patient with Hodgkin's disease. *Iran J Dermatol.* 2008;1:38–41.
- Narayanan G, Rekha Nair A, Somini Koshy E, et al. Cutaneous relapse in Hodgkin's disease. *Acta Oncol.* 1999;38:969–970.
- De Grip A, Schofield JB, Shotton JC. An unusual cutaneous presentation of Hodgkin's disease. *J Laryngol Otol.* 1999;113:765–768.
- Jain S, Nigam S, Kumar N, et al. Cutaneous relapse in Hodgkin's disease: a case report. *Acta Cytol.* 2005;49:191–194.
- Erkiliç Z, Erbagci Z, Koçer NE, et al. Cutaneous involvement in Hodgkin's lymphoma: report of two cases. *J Dermatol.* 2004;31:330–334.
- Cerroni L, Beham-Schmid C, Kerl H. Cutaneous Hodgkin's disease: an immunohistochemical analysis. *J Cutan Pathol.* 1995;22:229–235.
- Cho RJ, McCalmont TH, Ai WZ, et al. Use of an expanded immunohistochemical panel to distinguish cutaneous Hodgkin lymphoma from histopathologic imitators. *J Cutan Pathol.* 2012;39:651–658.
- Chang BK, Backstrand KH, Ng AK, et al. Significance of epithroclear lymph node involvement in Hodgkin disease. *Cancer.* 2001;91:1213–1218.